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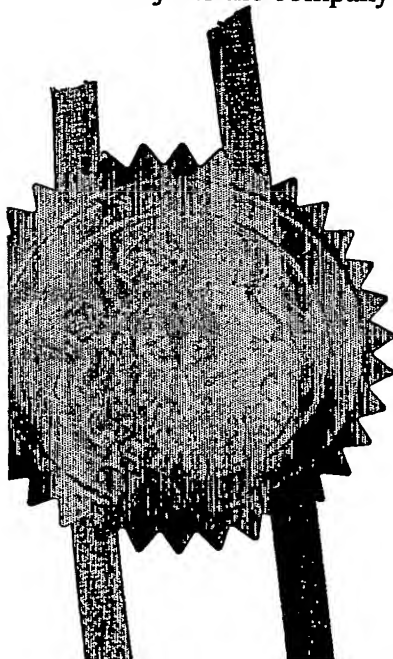
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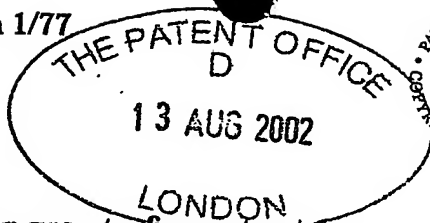


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Dated 10 September 2003

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Cardiff Road
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1. Your reference

0218800.1

PA 513

2. Patent application number

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13 AUG 2002

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CELTECH R & D LIMITED
208 BATH ROAD
SLOUGH
SL1 3WE

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

UK 8121485001

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

PATENTS DEPARTMENT
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SL1 3WE

Patents ADP number (if you know it)

8182305001

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Country

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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer Yes if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
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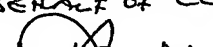
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10. If you are also filing any of the following, state how many against each item.

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11.

I/We request the grant of a patent on the basis of this application.
FOR + ON BEHALF OF CELETECH LTD LIMITED
Signature  Date 13th August 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr P. Ansell 01753 447566

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CHEMICAL COMPOUNDS

This invention relates to a series of 5-6 fused ring bicyclic heteroaromatic derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

Immune and inflammatory responses involve a variety of cell types with control and co-ordination of the various interactions occurring *via* both cell-cell contacts (e.g integrin interactions with their receptors) and by way of intercellular signalling molecules. A large number of different signalling molecules are involved including cytokines, lymphocytes, chemokines and growth factors.

Cells respond to such intercellular signalling molecules by means of intracellular signalling mechanisms that include protein kinases, phosphatases and phospholipases. There are five classes of protein kinase of which the major ones are the tyrosine kinases and the serine/threonine kinases [Hunter, T., Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T. and Sefton, B.M.; eds. Vol. 200, Academic Press; San Diego, 1991].

One sub-class of serine/threonine kinases is the mitogen activating protein (MAP) kinases of which there are at least three families which differ in the sequence and size of the activation loop [Adams, J. L. *et al*, Progress in Medicinal Chemistry p. 1-60, King, F. D. and Oxford, A. W.; eds. vol 38, Elsevier Science, 2001]: the extracellular regulated kinases (ERKs), the c-Jun NH₂ terminal kinases or stress activated kinases (JNKs or SAP kinases) and the p38 kinases which have a threonine-glycine-tyrosine (TGY) activation motif. Both the JNKs and p38 MAP kinases are primarily activated by stress stimuli including, but not limited to, proinflammatory cytokines e.g. tumour necrosis factor (TNF) and interleukin-1 (IL-1), ultraviolet light, endotoxin and chemical or osmotic shock.

Four isoforms of p38 have been described (p38 α / β / γ / δ). The human p38 α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially
5 termed CSAID binding protein-1 (CSBP-1) and CSBP-2 [Lee, J. C. *et al*,
Nature (London) 1994, 372, 739-46]. CSBP-2 is now widely referred to as
p38 α and differs from CSBP-1 in an internal sequence of 25 amino acids as
a result of differential splicing of two exons that are conserved in both mouse
and human [McDonnell, P. C. *et al*, Genomics 1995, 29, 301-2]. CSBP-1 and
10 p38 α are expressed ubiquitously and there is no difference between the two
isoforms with respect to tissue distribution, activation profile, substrate
preference or CSAID binding. A second isoform is p38 β which has 70%
identity with p38 α . A second form of p38 β termed p38 β 2 is also known and of
the two this is believed to be the major form. p38 α and p38 β 2 are expressed
15 in many different tissues. However in monocytes and macrophages p38 α is
the predominant kinase activity [Lee, J. C., *ibid*; Jing, Y. *et al*, J. Biol. Chem.
1996, 271, 10531-34; Hale, K. K. *et al*, J. Immun. 1999, 162, 4246-52]. p38 γ
and p38 δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have
~63% and ~61% homology to p38 α respectively. p38 γ is predominantly
20 expressed in skeletal muscle whilst p38 δ is found in testes, pancreas,
prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation
loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180
25 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is
essential for the activation of p38 and results in a >1000-fold increase in
specific activity of these enzymes [Doza, Y. N. *et al* FEBS Lett., 1995, 364,
7095-8012]. This dual phosphorylation is effected by MKK6 and under certain
conditions the related enzyme MKK3 [Enslin, H. *et al* J. Biol. Chem., 1998,
30 273, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed

MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.

- 5 Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF- β -activated kinase) are some of the enzymes identified as upstream activators of for MAPKKs.
- 10 MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H. Cell, 1998, 95, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor- β (TGF- β). TNF-stimulated activation of p38 is believed to be mediated by the
- 15 recruitment of TRAF2 [TNF receptor associated factor] and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

- Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38
- 20 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and
- 25 others substrates [e.g. cPLA2, p47phox].

- MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1,
- 30 IL-6, IFN-g and IL-10 is also partially inhibited [Kotlyarov, A. *et al* Nature Cell Biol. 1999, 1, 94-7]. Further, MAPKAP K2 from embryonic stem cells from

p38 α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. *et al*, J. Exp. Med. 2000, 191, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition
5 MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μ M
10 range [Lee, J. C. *et al*, Int. J. Immunopharm. 1988, 10, 835] and exhibits activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J. C. *et al*, Annals N. Y. Acad. Sci. 1993, 696, 149]. In addition these small molecule inhibitors are known to also decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8,
15 granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA2, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P. Trends Cell Biol. 1997, 7,
20 353-61].

A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis,
25 rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary
30 sarcoisosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to

acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS related complex.

5 Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition IL-1 has
10 been linked to diabetes and pancreatic β cells [Dinarello, C. A. J. Clinical Immunology, 1985, 5, 287-97].

IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF
15 and LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis which may contribute to increased
20 adhesion of neutrophils to vascular endothelial cells. Many diseases are characterised by massive neutrophil infiltration. Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysosomal enzyme release and respiratory burst from neutrophils.

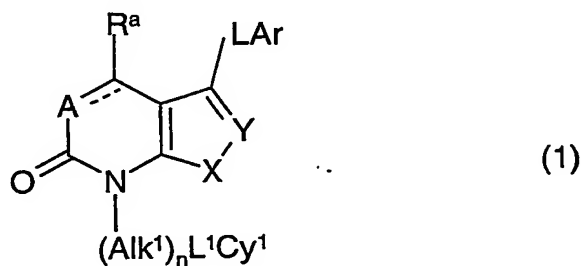
25 The central role of IL-1 and TNF together with other leukocyte derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

30

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling (see Figure 1) and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin) make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger, *et al*, J. Pharm. Exp. Ther. 1996, 279, 1453-61; Griswold, *et al*, Pharmacol. Comm., 1996, 7, 323-29].

We have now found a group of compounds which are potent and selective inhibitors of p38 kinase (p38 α , β , δ and γ) and the isoforms and splice variants thereof, especially p38 α , p38 β and p38 β 2. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

Thus according to one aspect of the invention we provide a compound of formula (1):



wherein:

the dashed line joining A and C(R^a) is present and represents a bond and

A is a $-N=$ atom or a $-C(R^b)=$ group, or the dashed line is absent and A is a $-N(R^b)-$, or $-C(R^b)(R^c)-$ group;

R^a , R^b and R^c is each independently a hydrogen atom or an optionally substituted C_{1-6} alkyl, $-CN$, $-CO_2H$, $-CO_2R^1$ (where R^1 is an optionally substituted alkyl group), $-CONH_2$, $-CONHR^1$ or $-CONR^1R^2$ group (where R^2 is an optionally substituted alkyl group);

X is an $-O-$, $-S-$ or substituted nitrogen atom or a $-S(O)-$, $-S(O_2)-$ or $-NH-$ group;

Y is a nitrogen or substituted carbon atom or a $-CH=$ group;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain

L^1 is a covalent bond or a linker atom or group;

Cy^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

L is an atom or chain $-(CH_2)_pHet(CH_2)_q-$ in which p and q, which may be the same or different, is each zero or the integer 1 and Het is an $-O-$ or $-S-$ atom or a $-C(R^{3a})(R^{3b})-$ (where R^{3a} and R^{3b} , which may be the same or different, is each a hydrogen atom or an $-OH$ or optionally substituted C_{1-6} alkyl group), $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(S)-$, $-S(O)-$, $-S(O)_2-$, $-N(R^{3c})O-$ [where R^{3c} is a hydrogen atom or a straight or branched alkyl group], $-N(R^{3c})N-$, $-CON(R^{3c})-$, $-OC(O)N(R^{3c})-$, $-CSN(R^{3c})-$, $-N(R^{3c})CO-$, $-N(R^{3c})C(O)O-$, $-N(R^{3c})CS-$, $-S(O)_2N(R^{3c})-$, $-N(R^{3c})S(O)_2-$, $-N(R^{3c})CON(R^{3d})-$ (where R^{3d} is as defined for R^{3c} and may be the same or different), $-N(R^{3c})CSN(R^{3d})-$ or $-N(R^{3c})SO_2N(R^{3d})-$ group and, when one or both of p and q is the integer 1, Het is additionally a $-N(R^{3c})-$ group;

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof;

It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to

be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist
5 as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$)-enol ($\text{CH}=\text{CHOH}$) tautomers.

----- Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise. -----

As used in formula (1) the terms "substituted nitrogen atom" and "substituted
10 carbon atom" are intended to include groups such as those in which X is $-\text{N}(\text{R}^{10})-$ and Y is $-\text{C}(\text{R}^{10})=$ where R^{10} is a substituent other than a hydrogen atom as generally or particularly defined hereinafter.

The following general terms as used herein in relation to compounds of the
15 invention and intermediates thereto have the stated meaning below unless specifically defined otherwise.

Thus as used herein the term "alkyl" whether present as a group or part of a group includes straight or branched C_{1-6} alkyl groups, for example C_{1-4} alkyl
20 groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl or t-butyl groups. Similarly, the terms "alkenyl" or "alkynyl" are intended to mean straight or branched C_{2-6} alkenyl or C_{2-6} alkynyl groups such as C_{2-4} alkenyl or C_{2-4} alkynyl groups. Optional substituents which may be present on these groups include those optional substituents mentioned hereinafter in relation
25 to Alk^1 when Alk^1 is an optionally substituted aliphatic chain.

The term halogen is intended to include fluorine, chlorine, bromine or iodine atoms.

30 The term "haloalkyl" is intended to include those alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular

examples of such groups include $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CHF}_2$, $-\text{CHCl}_2$, $-\text{CH}_2\text{F}$ and $-\text{CH}_2\text{Cl}$ groups.

5 The term "alkoxy" as used herein is intended to include straight or branched C_{1-6} alkoxy e.g. C_{1-4} alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCH}_2\text{F}$ and $-\text{OCH}_2\text{Cl}$ groups.

10

As used herein the term "alkylthio" is intended to include straight or branched C_{1-6} alkylthio, e.g. C_{1-4} alkylthio such as methylthio or ethylthio.

15 As used herein the term "alkylamino or dialkylamino" is intended to include the groups $-\text{NHR}^{1a}$ and $-\text{N}(\text{R}^{1a})(\text{R}^{1b})$ where R^{1a} and R^{1b} is each independently an optionally substituted straight or branched alkyl group or both together with the N atom to which they are attached form an optionally substituted heterocycloalkyl group which may contain a further heteroatom or heteroatom containing group such as an $-\text{O}-$ or $-\text{S}-$ atom or $-\text{N}(\text{R}^{1a})-$ group.

20 Particular examples of such optionally substituted heterocycloalkyl groups include optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and $\text{N}'\text{-C}_{1-6}$ alkyl-piperazinyl groups. The optional substituents which may be present on such heterocycloalkyl groups include those optional substituents as described hereinafter in relation to aliphatic chains such as

25 Alk^1 .

When Alk^1 is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene,

30 C_{2-6} alkenylene, or C_{2-6} alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}_2-$, $-(\text{CH}_2)_3\text{CH}_2-$, $-\text{CH}(\text{CH}_3)(\text{CH}_2)_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$,
 5 $\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_4\text{CH}_2-$, $-(\text{CH}_2)_5\text{CH}_2-$, $-\text{CHCH}-$, $-\text{CHCHCH}_2-$, $-\text{CH}_2\text{CHCH}-$, $-\text{CHCHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CHCHCH}_2-$,

 $(\text{CH}_2)_2\text{CHCH}-$, $-\text{CC}-$, $-\text{CCCH}_2-$, $-\text{CH}_2\text{CC}-$, $-\text{CCCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CCCH}_2-$ or $-(\text{CH}_2)_2\text{CCH}-$ chains.

- 10 Heteroaliphatic chains represented by Alk^1 in the compounds of formula (1) include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be
 15 positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-\text{L}^2\text{CH}_2-$, $-\text{CH}_2\text{L}^2-$, $-\text{L}^2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{L}^2-$, $-\text{CH}_2\text{L}^2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{L}^2-$, $-\text{CH}_2\text{CH}_2\text{L}^2-$, $-\text{CH}_2\text{L}^2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{L}^2\text{CH}_2\text{CH}_2\text{L}^2-$, $-(\text{CH}_2)_2\text{L}^2\text{CH}_2-$, $-(\text{CH}_2)_3\text{L}^2\text{CH}_2-$, $-\text{L}^2(\text{CH}_2)_2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CHCH}-$, $-\text{CHCHCH}_2\text{L}^2-$ and
 20 $-(\text{CH}_2)_2\text{L}^2\text{CH}_2\text{CH}_2-$ chains.

When L^2 is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^3)-$ [where R^3
 25 is a hydrogen atom or a straight or branched alkyl group], $-\text{N}(\text{R}^3)\text{O}-$, $-\text{N}(\text{R}^3)\text{N}-$, $-\text{CON}(\text{R}^3)-$, $-\text{OC}(\text{O})\text{N}(\text{R}^3)-$, $-\text{CSN}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{CO}-$, $-\text{N}(\text{R}^3)\text{C}(\text{O})\text{O}-$, $-\text{N}(\text{R}^3)\text{CS}-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^3)\text{CON}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{CSN}(\text{R}^3)-$ or $-\text{N}(\text{R}^3)\text{SO}_2\text{N}(\text{R}^3)-$ groups. Where L^2 contains two R^3 groups these may be the same or different.

30

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or $-\text{OH}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^4$ [where R^4 is an optionally substituted straight or branched C_{1-6} alkyl group], e.g. $-\text{CO}_2\text{CH}_3$ or $-\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{CONHR}^4$, e.g. $-\text{CONHCH}_3$, $-\text{CON}(\text{R}^4)_2$, e.g. $-\text{CON}(\text{CH}_3)_2$, $-\text{COR}^4$, e.g. $-\text{COCH}_3$, C_{1-6} alkoxy, e.g. methoxy or ethoxy, halo C_{1-6} alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol ($-\text{SH}$), $-\text{S}(\text{O})\text{R}^4$, e.g. $-\text{S}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{R}^4$, e.g. $-\text{S}(\text{O})_2\text{CH}_3$, C_{1-6} alkylthio e.g. methylthio or ethylthio, amino, $-\text{NHR}^4$, e.g. $-\text{NHCH}_3$ or $-\text{N}(\text{R}^4)_2$, e.g. $-\text{N}(\text{CH}_3)_2$ groups. Where two R^4 groups are present in any of the above substituents these may be the same or different.

In addition when two R^4 alkyl groups are present in any of the optional substituents just described these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom containing group selected from $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^4)-$, $-\text{C}(\text{O})-$ or $-\text{C}(\text{S})-$ groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When L^1 is present in compounds of formula (1) as a linker atom or group it may be any such atom or group as hereinbefore described in relation to L^2 linker atoms and groups.

Optionally substituted cycloaliphatic groups represented by the group Cy^1 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g. C_{3-7} cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group Cy¹ include optionally substituted C₃₋₁₀heterocycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀heterocycloalkyl, e.g. C₃₋₇heterocycloalkyl or C₃₋₁₀heterocycloalkenyl, e.g. C₃₋₇heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom containing groups L⁴ in place of or in addition to the ring carbon atoms where L⁴ is an atom or group as previously defined for L².

Optionally substituted polycycloaliphatic groups represented by the group Cy¹ include optionally substituted C₇₋₁₀bi- or tricycloalkyl or C₇₋₁₀bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group Cy¹ include optionally substituted C₇₋₁₀bi- or tricycloalkyl or C₇₋₁₀bi- or tri-cycloalkenyl groups containing one, two, three, four or more L⁴ atoms or groups in place of or in addition to the ring carbon atoms.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group Cy¹ include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, 5,6-dihydro-2(1H)-pyrazinone, tetrahydropyrimidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, 1,3,5-oxadiazinyl,

dihydroisothiazolyl, dihydroisothiazole 1,1-dioxide, e.g. 2,3-dihydroisothiazole 1,1-dioxide, dihydropyrazinyl and tetrahydropyrazinyl groups.

- 5 The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group Cy^1 include one, two, three or more substituents selected from halogen atoms, or C_{1-6} alkyl, e.g. methyl or ethyl, halo C_{1-6} alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl,
- 10 optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6} alkoxy, e.g. methoxy or ethoxy, halo C_{1-6} alkoxy, eg. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C_{1-6} alkylthiol, e.g. methylthiol or ethylthiol, carbonyl ($=O$), thiocarbonyl ($=S$), imino ($=NR^{4a}$) [where R^{4a} is an $-OH$ group or a C_{1-6} alkyl group], or $-(Alk^3)_vR^5$ groups in which Alk^3 is a straight
- 15 or branched C_{1-3} alkylene chain, v is zero or the integer 1 and R^5 is a C_{3-8} cycloalkyl, $-OH$, $-SH$, $-N(R^6)(R^7)$ [in which R^6 and R^7 is each independently selected from a hydrogen atom or an optionally substituted alkyl or C_{3-8} cycloalkyl group], $-OR^6$, $-SR^6$, $-CN$, $-NO_2$, $-CO_2R^6$, $-SOR^6$, $-SO_2R^6$, $-SO_3R^6$, $-OCO_2R^6$, $-C(O)R^6$, $-OC(O)R^6$, $-C(S)R^6$, $-C(O)N(R^6)(R^7)$, $-OC(O)N(R^6)(R^7)$,
- 20 $N(R^6)C(O)R^7$, $-C(S)N(R^6)(R^7)$, $-N(R^6)C(S)R^7$, $-SO_2N(R^6)(R^7)$, $-N(R^6)SO_2R^7$, $-N(R^6)C(O)N(R^7)(R^8)$ [where R^8 is as defined for R^6], $-N(R^6)C(S)N(R^7)(R^8)$, $-N(R^6)SO_2N(R^7)(R^8)$ or an optionally substituted aromatic or heteroaromatic group.
- 25 Particular examples of Alk^3 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$ chains.

When R^5 , R^6 , R^7 and/or R^8 is present as a C_{3-8} cycloalkyl group it may be for example a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional

30 substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from

halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆alkoxy, e.g. methoxy, ethoxy or *i*-propoxy groups.

When the groups R⁶ and R⁷ or R⁷ and R⁸ are both alkyl groups these groups
5 may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a
further heteroatom or heteroatom containing group selected from -O-, -S-, -N(R⁷)-, -C(O)- or -C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl,
10 pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When R⁵ is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter in relation to Cy¹.

15 Additionally, when the group Cy¹ is a heterocycloaliphatic or heteropolycycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group -(L⁵)_p(Alk⁴)_qR⁹ in which L⁵ is a -C(O)-, -C(O)O-, -C(S)-, -S(O)₂-, -CON(R⁶)- or -SO₂N(R⁶)- group; p is zero or the integer 1; Alk⁴ is an optionally substituted aliphatic or
20 heteroaliphatic chain; q is zero or the integer 1; and R⁹ is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group as herein described in relation to Cy¹.

25 When Alk⁴ is present as an aliphatic or heteroaliphatic chain it may be for example any aliphatic or heteroaliphatic chain as hereinbefore described for Alk¹.

Optionally substituted aromatic groups represented by the groups Cy¹ include
30 for example monocyclic or bicyclic fused ring C₆₋₁₂aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Heteroaromatic groups represented by the groups Cy¹ include for example C₁₋₉heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the
5 heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-
10 membered fused ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl,
15 isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, [2,3-dihydro]benzothienyl, benzotriazolyl, indolyl, indolinyl, indazolyl, benzimidazolyl, imidazo[1,2-
20 a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,5-a]pyridinyl, imidazo[1,5-a]pyrazinyl, imidazo[1,5-c]pyrimidinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-
25 tetrahydroisoquinolinyl, imidyl, e.g. succinimidyl, phthalimidyl or naphthalimidyl such as 1,8-naphthalimidyl, pyrazolo[4,3-d]pyrimidinyl, furo[3,2-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, pyrrolo[3,2-d]pyrimidinyl, pyrazolo[3,2-b]pyridinyl, furo[3,2-b]pyridinyl, thieno[3,2-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, thiazolo[3,2-a]pyridinyl, pyrido[1,2-a]pyrimidinyl,
30 tetrahydroimidazo[1,2-a]pyrimidinyl and dihydroimidazo[1,2-a]pyrimidinyl groups.

Optional substituents which may be present on aromatic or heteroaromatic groups represented by the group Cy^1 include one, two, three or more substituents, each selected from an atom or group R^{10} in which R^{10} is R^{10a} or

5 $-L^6Alk^5(R^{10a})_r$, where R^{10a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl ($-OH$), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{11}$ [where R^{11} is an $-L^6Alk^3(R^{10a})_r$, aryl or heteroaryl group], $-CSR^{11}$, $-SO_3H$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-SO_2NH_2$, $-SO_2NHR^{11}$, $-SO_2N(R^{11})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{11}$, $-$

10 $CSNHR^{11}$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-N(R^{12})SO_2R^{11}$ [where R^{12} is a hydrogen atom or a straight or branched alkyl group], $-N(SO_2R^{11})_2$, $-N(R^{12})SO_2NH_2$, $-N(R^{12})SO_2NHR^{11}$, $-N(R^{12})SO_2N(R^{11})_2$, $-N(R^{12})COR^{11}$, $-N(R^{12})CONH_2$, $-N(R^{12})CONHR^{11}$, $-N(R^{12})CON(R^{11})_2$, $-N(R^{12})CSNH_2$, $-N(R^{12})CSNHR^{11}$, $-N(R^{12})CSN(R^{11})_2$, $-N(R^{12})CSR^{11}$, $-N(R^{12})C(O)OR^{11}$, $-SO_2NHet^1$ [where $-$

15 $NHet^1$ is an optionally substituted C_{5-7} cyclicamino group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^{12})-$, $-C(O)-$ or $-C(S)-$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{12})SO_2NHet^1$, $-N(R^{12})CONHet^1$, $-N(R^{12})CSNHet^1$, $-SO_2N(R^{12})Het^2$ [where $-Het^2$ is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more other $-O-$ or $-S-$ atoms

20 or $-N(R^{12})-$, $-C(O)-$, $-S(O)-$ or $-S(O)_2-$ groups], $-Het^2$, $-CON(R^{12})Het^2$, $-CSN(R^{12})Het^2$, $-N(R^{12})CON(R^{12})Het^2$, $-N(R^{12})CSN(R^{12})Het^2$, $-N(R^{12})SO_2N(R^{12})Het^2$, aryl or heteroaryl groups; L^6 is a covalent bond or a linker atom or group as hereinbefore defined for L^2 ; Alk^5 is an optionally substituted straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three $-O-$ or $-S-$ atoms or $-S(O)_n-$ [where n is an integer 1 or 2] or $-N(R^{12})-$ e.g. $-N(CH_3)-$ groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

When in the group $-L^6Alk^5(R^{10a})_r$, r is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{10a} may be present on any suitable carbon atom in $-Alk^5$. Where more than one R^{10a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^5$. Clearly, when r is zero and no substituent R^{10a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^5 becomes an alkyl, alkenyl or alkynyl group.

When R^{10a} is a substituted amino group it may be for example a group $-NHR^{11}$ [where R^{11} is as defined above] or a group $-N(R^{11})_2$ wherein each R^{11} group is the same or different.

When R^{10a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{10a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{11}$ or a $-SR^{12}$ group respectively.

Esterified carboxyl groups represented by the group R^{10a} include groups of formula $-CO_2Alk^6$ wherein Alk^6 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroxyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^6 group include R^{10a} atoms and groups as described above.

When Alk^5 is present in or as a substituent it may be for example a $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$,
 5 $\text{CH}=\text{CH}-$, $-\text{CH}=\text{CCH}_2-$, $-\text{CH}_2\text{C}=\text{CH}-$, $-\text{CH}=\text{CHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2-$, $-\text{CC}-$, $-\text{CCCH}_2-$, $-\text{CH}_2\text{CC}-$, $-\text{CCCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CCCH}_2-$ or ~~-----~~
~~-----~~ $\text{CH}_2\text{CH}_2\text{CC}-$ chain, optionally interrupted by one, two, or three $-\text{O}-$ or $-\text{S}-$, atoms or $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$ or $-\text{N}(\text{R}^{12})-$, e.g. $-\text{N}(\text{CH}_3)-$ groups. The aliphatic chains represented by Alk^5 may be optionally substituted by one, two or three halogen
 10 atoms in addition to any R^{10a} groups that may be present.

Aryl or heteroaryl groups represented by the groups R^{10a} or R^{11} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Cy^1 . The aromatic and heteroaromatic groups
 15 may be attached to the group Cy^1 in compounds of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

It will be appreciated that when $-\text{NHet}^1$ or $-\text{Het}^2$ forms part of a substituent R^{10} the heteroatoms or heteroatom containing groups that may be present within the
 20 ring $-\text{NHet}^1$ or $-\text{Het}^2$ take the place of carbon atoms within the parent carbocyclic ring.

Thus when $-\text{NHet}^1$ or $-\text{Het}^2$ forms part of a substituent R^{10} each may be for example an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl,
 25 piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-\text{NHet}^1$ include those substituents described above when Cy^1 is a heterocycloaliphatic group.

30

Particularly useful atoms or groups represented by R¹⁰ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl,

5 carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₃₋₇cycloalkyl, e.g. cyclobutyl, cyclopentyl, C₅₋

10 ₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino, -CH(CH₃)NH₂ or -C(CH₃)₂NH₂, haloC₁₋₆alkylamino, e.g. fluoroC₁₋₆alkylamino, e.g. -CH(CF₃)NH₂ or -C(CF₃)₂NH₂, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋

15 ₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano,

20 hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁶ [where Alk⁶ is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋

25 ₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylamino-carbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g.

30 diethylaminoethyl-aminocarbonyl, aminocarbonylamino, C₁₋alkylaminocarbonylamino, e.g. methylaminocarbonylamino or

ethylaminocarbonylamino, C₁₋₆dialkylamino-carbonylamino, e.g.
dimethylaminocarbonylamino or diethylamino-carbonylamino, C₁₋₆
alkylaminocarbonylC₁₋₆alkylamino, e.g. methylamino-carbonylmethylamino,
aminothiocarbonylamino, C₁₋₆alkylaminothiocarbonyl-amino, e.g.
5 methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆
dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or
diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g.
ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonyl-
amino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkyl-
10 sulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino,
optionally substituted phenylsulphonylamino, aminosulphonylamino (-
NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino
or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethyl-
aminosulphonylamino or diethylaminosulphonylamino, optionally substituted
15 morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally
substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino,
aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoyl-
amino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g.
acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethyl-
20 amino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonyl-
amino or t-butoxycarbonylamino or optionally substituted benzyloxy,
pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxy-
carbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, benzothio, pyridyl-
methylthio or thiazolylmethylthio groups.

25

A further particularly useful group of substituents represented by R¹⁰ when
present on aromatic or heteroaromatic groups includes substituents of formula -
L⁶Alk⁵R^{10a} where L⁶ is preferably a covalent bond or an -O- or -S- atom or -
N(R³)-, -C(O)-, -C(O)O-, -O-C(O)-, -N(R³)CO-, -CON(R³)- or -N(R³)S(O)₂-
30 group, Alk⁵ is an optionally substituted C₁₋₆alkyl group optionally interrupted by
one or two -O- or -S- atoms or -N(R¹²)-, -C(O)-, -C(S)-, -CON(R¹²)- or -

$N(R^{12})CO-$ groups and R^{10a} is an optionally substituted Het^2 group as herein defined or an optionally substituted heteroaromatic group as hereinbefore described in relation to Cy^1 .

- 5 Where desired, two R^{10} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6} alkylenedioxy group such as methylenedioxy or ethylenedioxy.

- 10 It will be appreciated that where two or more R^{10} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group represented by the group Cy^1 .

- 15 The substituted aromatic or heteroaromatic group represented by Ar in compounds of the invention may be any aromatic or heteroaromatic group as hereinbefore described for Cy^1 . Optional substituents which may be present include those R^{10} atoms and groups as generally or particularly described in relation to Cy^1 aromatic and heteroaromatic groups.

- 20 In general in compounds of formula (1) X is preferably an -O- or -S- atom, and is especially a -S- atom.

- In another group of compounds of formula (1) R^a is preferably a hydrogen atom or a C_{1-4} alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. In particular R^a is a methyl group or more especially a hydrogen atom.
- 25

- In another particular class of compounds of formula (1) the bond represented by the dashed line is present and A is a $-C(R^b)=$ group. In these compounds R^b is preferably a hydrogen atom or a C_{1-4} alkyl group, especially a methyl, ethyl, n-propyl or i-propyl group. More particularly R^b is a methyl group or more especially a hydrogen atom.
- 30

When in compounds of formula (1) n is the integer 1, Alk^1 is preferably an optionally substituted C_{1-6} alkylene chain, especially an optionally substituted $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$ or $-\text{CH}_2\text{CH}(\text{CH}_3)-$ chain,
5 most especially a $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$ chain.

In one class of compounds of formula (1) n is zero.

The group L^1 in compounds of formula (1) is preferably a covalent bond or an
10 $-\text{O}-$ or $-\text{S}-$ atom or an $-\text{N}(\text{R}^3)-$, especially $-\text{NH}-$ or $-\text{N}(\text{CH}_3)-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$ group. More particularly L^1 is a covalent bond or an $-\text{O}-$ or $-\text{S}-$ atom or $-\text{NH}-$ group. L^1 is more especially preferably is a covalent bond.

Cy^1 in compounds of formula (1) is preferably an optionally substituted
15 cycloaliphatic, aromatic or heteroaromatic group as hereinbefore generally and particularly defined.

Particularly preferred Cy^1 optionally substituted cycloaliphatic groups include optionally substituted C_{3-7} cycloalkyl groups, especially cyclopropyl,
20 cyclobutyl, cyclopentyl or cyclohexyl groups.

Particularly preferred optional substituents which may be present on Cy^1 optionally substituted cycloaliphatic groups include halogen atoms, especially fluorine, chlorine or bromine atoms, or C_{1-6} alkyl groups, especially C_{1-3} alkyl
25 groups, most especially a methyl group, or a halo C_{1-6} alkyl group, especially a fluoro C_{1-6} alkyl group, most especially a $-\text{CF}_3$ group, or a C_{1-6} alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a halo C_{1-6} alkoxy, especially a fluoro C_{1-6} alkoxy, most especially a $-\text{OCF}_3$ group, or a cyano ($-\text{CN}$), esterified carboxyl, especially $-\text{CO}_2\text{CH}_3$ or $-\text{CO}_2\text{C}(\text{CH}_3)_3$, nitro ($-\text{NO}_2$),
30 amino ($-\text{NH}_2$), substituted amino, especially $-\text{NHCH}_3$ or $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{R}^6$, especially $-\text{C}(\text{O})\text{CH}_3$, or $-\text{N}(\text{R}^6)\text{C}(\text{O})\text{R}^7$, especially $-\text{NHCOCH}_3$ group.

Particularly preferred Cy¹ aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially
5 optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

10

Particularly preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r, as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C₁-
15 ₆alkyl groups, especially C₁₋₃alkyl groups, most especially a methyl group, or a haloC₁₋₆alkyl group, especially a fluoroC₁₋₆alkyl group, most especially a -CF₃ group, or a C₁₋₆alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a -OCF₃ group, or a cyano (-CN), carboxyl (-CO₂H), esterified carboxyl (-
20 CO₂Alk⁶), especially -CO₂CH₃, -CO₂CH₂CH₃, or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃ group.

Further preferred optional substituents which may be present on Cy¹
25 aromatic or heteroaromatic groups include groups of formula -L⁶Alk⁵(R^{10a})_r, in which r is the integer 1, L⁶ is a covalent bond or an -O- or -S- atom or a -N(R³)-, especially -NH- or -N(CH₃)-, -C(O)-, -C(S)-, -C(O)O-, -OC(O)-, -N(R³)CO-, especially -NHCO-, or -CON(R³)-, especially -CHNH-group, Alk⁵ is a C₁₋₆alkyl chain, especially a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- or -
30 CH₂CH₂CH₂CH₂- chain and R^{10a} is a substituted hydroxyl group, especially a -OCH₃, -OCH₂CH₃ or -OCH(CH₃)₂ group or a substituted amino group,

especially a $-N(CH_3)_2$ or $-N(CH_2CH_3)_2$ group or a $-Het$ group, especially an optionally substituted monocyclic C_{5-7} carbocyclic group containing one, two or three $-O-$, $-S-$, $-N(R^{12})-$, especially $-NH-$ or $-N(CH_3)-$ or $-C(O)-$ groups within the ring structure as previously described, most especially an
 5 optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. N-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group or R^{10a} is
 an optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms, such as
 10 optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, triazinyl, pyridazinyl, or pyrazinyl group. Particularly preferred optional substituents on the $-Het$ groups just described include hydroxyl ($-OH$) and carboxyl ($-CO_2H$) groups or those preferred optional substituents just described in relation to the group Cy^1 .

15 In one particularly preferred group of compounds of formula (1) Cy^1 is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three optional substituents where at least one, and preferably two optional substituents are located *ortho* to the bond joining Cy^1 to the remainder of the compound of formula (1), (1a) or (2a). Particularly
 20 preferred *ortho* substituents include halogen atoms, especially fluorine or chlorine atoms, or C_{1-3} alkyl groups, especially methyl groups, C_{1-3} alkoxy groups, especially methoxy, halo C_{1-3} alkyl groups, especially $-CF_3$, halo C_{1-3} alkoxy groups, especially $-OCF_3$, or cyano ($-CN$), groups. In this class of compounds a second or third optional substituent when present in a position
 25 other than the *ortho* positions of the ring Cy^1 may be preferably an atom or group $-R^{10a}$ or $-L^6Alk^5(R^{10a})_r$ as herein generally and particularly described.

The group Y in compounds of formula (1) is preferably a $-CH=$ group or a substituted carbon atom. Particular substituted carbon atoms include those where Y is $-C(R^{10})=$ wherein R^{10} is as generally or particularly described
 30 above, especially those $-R^{10a}$ and $-L^6Alk^5(R^{10a})_r$ substituents just described

with respect to those preferred optional substituents present on Cy¹ aromatic or heteroaromatic groups. Particularly useful compounds of formula (1) are those compounds wherein Y is -CH= or -C(R¹⁰)= in which R¹⁰ is a -CN, -CONH₂, -CONHR¹¹, -CON(R¹¹)₂, -CONHet¹, -CON(R¹²)Het, 5 -CON(R¹²)Alk⁵Het, or esterified carboxyl, particularly -CO₂Alk⁶ group as generally or particularly described herein.

LAr in compounds of the invention may in particular be an -OAr, -SAr, -C(R^{3a})(R^{3b})Ar, especially -CH₂Ar, or -N(R^{3c})CH₂Ar, especially -NHCH₂Ar 10 group.

Particularly preferred Ar aromatic groups in compounds of formula (1) include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, 15 especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl or triazinyl group.

20 Particularly preferred optional substituents which may be present on Ar aromatic or heteroaromatic groups include atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r, as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, or C₁₋₆alkyl groups, especially C₁₋₃alkyl groups, most especially a methyl group, or 25 a haloC₁₋₆alkyl group, especially a fluoroC₁₋₆alkyl group, most especially a -CF₃ group, or a C₁₋₆alkoxy, especially methoxy, ethoxy, propoxy or i-propoxy group, or a haloC₁₋₆alkoxy, especially a fluoroC₁₋₆alkoxy, most especially a -OCF₃ group, or a cyano (-CN), esterified carboxyl, especially -CO₂CH₃ or -30 CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -

NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃ group.

Particularly useful Ar groups in compounds of formula (1) include phenyl and
5 mono- or disubstituted phenyl groups in which each substituent is in particular a -R^{10a} or -L⁶Alk⁵(R^{10a})_r atom or group as just defined and is especially a halogen atom or a C₁₋₃alkyl, C₁₋₃alkoxy or -CN group

Particularly useful compounds of the invention include each of the
10 compounds described in the Examples hereinafter, and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent and selective inhibitors of p38 kinases, including all isoforms and splice variants thereof. More
15 specifically the compounds of the invention are inhibitors of p38 α , p38 β and p38 β 2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

20 The compounds of formula (1) are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Further
25 the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating any such disease or disorder.

The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by
30 excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a

human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further the invention extends to the administration to a human an effective amount of a p38 inhibitor for treating
5 any such disease or disorder.

Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8 include without limitation autoimmune diseases, inflammatory diseases,
10 destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2
15 (COX-2).

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic
20 lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs, host disease or psoriasis.

25 The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome or acute or chronic
30 pancreatitis.

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

- 5 Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma and multiple myeloma.
-

- 10 Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury.

- 15 Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

- 20 In addition, p38 inhibitors of this invention also exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2) and are therefore of use in therapy. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid are produced by
- 25 inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors,
- 30 or edema. Accordingly additional p38 mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as

neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

5 As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

10 Thus TNF mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to
15 infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, viral infections such as HIV, CMV, influenza and herpes; and veterinary viral infections, such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; or
20 retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Compounds of the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to
25 upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the TNF inhibiting compounds of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the
30 Herpes group of viruses such as Herpes Zoster and Herpes Simplex.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, diabetes, pancreatic
5 β -cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis,
10 inflammatory bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The increased IL-8 production associated with each of these diseases is responsible for the chemotaxis of neutrophils into inflammatory sites. This is due to the unique property of IL-8 (in comparison
15 to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in neutrophil infiltration.

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV)
20 infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al*, Clin. Infect. Dis., 1997, 26, 840; Grunberg *et al*, Am. J. Crit. Care Med. 1997, 155, 1362; Zhu *et al*, J. Clin. Invest. 1996, 97, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the
25 primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al*, J. Clin. Invest. 1995, 96, 549]. Therefore, p38 inhibitors of the invention may be used for the treatment or prophylaxis of the common cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus,
30 respiratory syncytial virus or adenovirus infection.

For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine mediated disease the compounds according to the invention may be administered to a human or mammal as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

- 5 The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.
- 10
- 15 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.
- 20 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.
- 25

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

30

For topical administration the compounds for use according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example,
5 mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively the compounds for use according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for
10 example mineral oil, sorbitan monostearate, polysorbate 60, cetyl ester's wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds for use according to the present invention may be conveniently formulated as microionized
15 suspensions in isotonic, pH adjusted sterile saline, either with or without a preservative such as bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

20

For rectal administration the compounds for use according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature
25 and so will melt in the rectum to release the active component. Such materials include for example cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or
30 treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however,

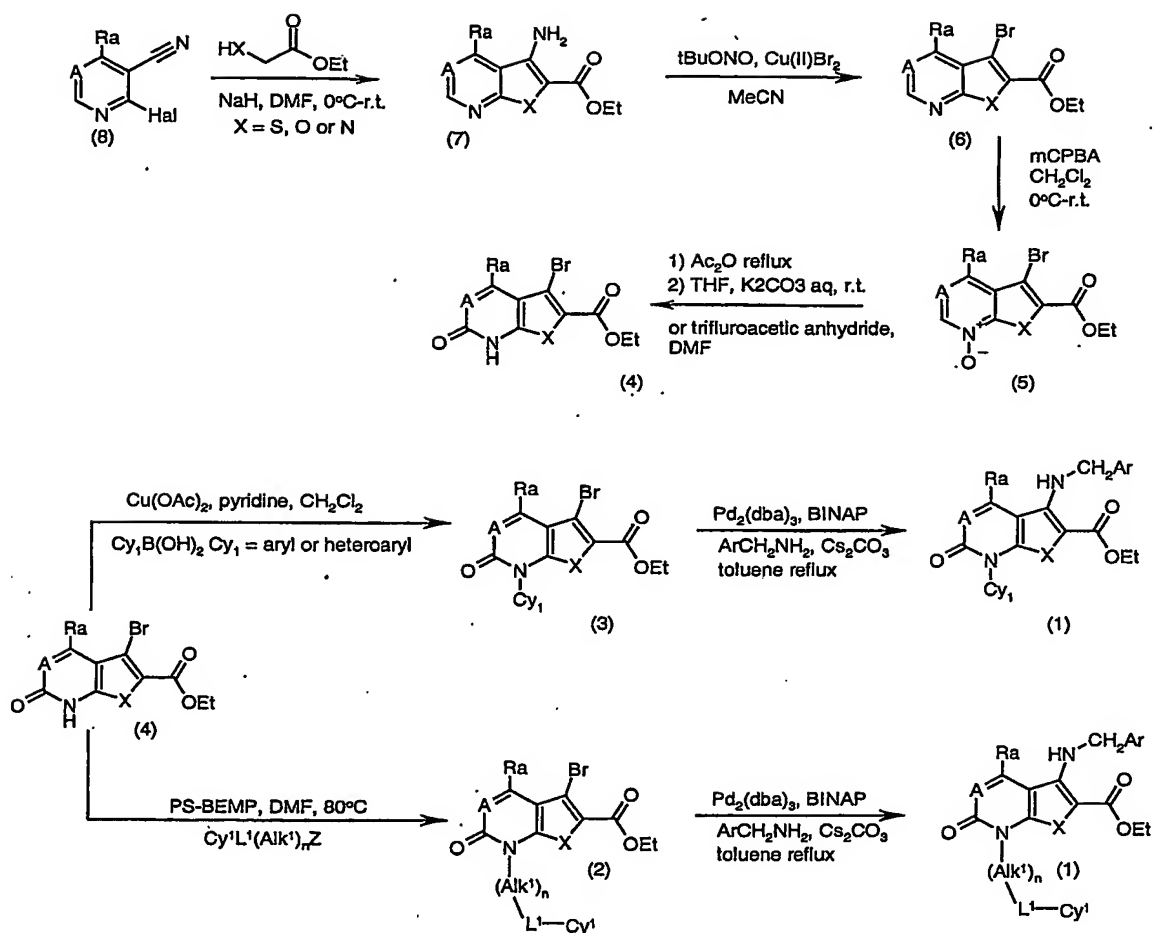
daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, Cy¹, Alk¹, n, L¹, L, R^a, R^b, R^c, A, X and Y when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention a compound of formula (1) in which A is a $-C(R^b)=$ group, X is a $-O-$ or $-S-$ atom or $-NH-$ group, Y is a substituted carbon atom in which the substituent is an esterified carboxyl group, for example a $-CO_2Alk^6$ group, and L is a $-NHCH_2-$ chain may be prepared according to the reactions set out in Scheme 1 below. In the Scheme the preparation of an ethyl ester is specifically shown, but it will be appreciated that other esters may be obtained by simply varying the ester starting material and if appropriate any reaction conditions:

Scheme 1

5



Thus in Scheme 1 a compound of formula (1) may be prepared by reaction of a compound of formulae (2) or (3) with an amine ArCH_2NH_2 in the presence of a palladium catalyst. The reaction may be conveniently carried out in a solvent such as toluene at an elevated temperature, eg the reflux temperature, using a catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and a base such as caesium

carbonate. Where desired, alternative reaction conditions may be used, for example as described in the literature [Luker et al. Tet. Lett. (2001) 41, 7731; Buchwald S.L. J.Org.Chem. (2000) 65 1144; Hartwig J.F. Angew. Chem. Int. Ed. Engl. (1998) 37, 2046].

5

Intermediates of formula (2) may be prepared by reaction of a compound of formula (4) with an alkylating agent of formula $Cy^1L^1(Alk^1)_nZ$, where Z is a leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy e.g. phenylsulphonyloxy group.

The reaction may be performed in the presence of a solvent, for example a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an inorganic base such as sodium hydride, or an organic base such as an organic amine, e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene or a resin bound organic amine such as resin bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (PS-BEMP), at an elevated temperature, for example 80 to 100°C.

Intermediates of formula (3) may be prepared by the reaction of a compound of formula (4) with a boronic acid of formula $Cy^1B(OH)_2$ in which Cy^1 is an aryl or heteroaryl group. The reaction may be performed in an organic solvent, for example a halogenated hydrocarbon such as dichloromethane or dichloroethane in the presence of a copper reagent, for example a copper (II) reagent such as copper (II) acetate, optionally in the presence of an oxidant, for example 2,2,6,6-tetramethyl-1-piperidinyloxy or pyridine-N-oxide, optionally in the presence of a base, for example an organic amine such as an alkylamine, e.g. triethylamine or an aromatic amine, e.g. pyridine at a temperature from around ambient to the reflux temperature [see for example

Chan, D.T. *et al* Tetrahedron Letters, 1998, 2933; Lam, P.Y.S. *et al*, Tetrahedron Letters, 2001, 3415]

5 It will be appreciated that if desired the reactions just described may be carried out in the reverse order so that the amination using ArCH_2NH_2 is performed first with the intermediate of formula (4) followed by alkylation/arylation to yield the compound of formula (1).

10 Intermediate pyridinones of formula (4) may be prepared from pyridine N-oxides of formula (5) by sequential reaction with an anhydride, for example acetic anhydride at an elevated temperature, for example the reflux temperature followed by reaction with an inorganic base, for example a carbonate such as aqueous potassium carbonate in a solvent such as an ether for example a cyclic ether e.g. tetrahydrofuran at around ambient
15 temperature. Alternatively the reaction may be performed using trifluoroacetic anhydride in dimethylformamide from 0°C to ambient temperature conditions [see for example Konno et al., Heterocycles (1986) 24, 2169].

20 Pyridine N-oxides of formula (5) may be formed by oxidation of pyridines of formula (6) using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C , or alternatively by reaction with a peracid such as peracetic acid or m-chloroperoxybenzoic acid in a solvent, such as a halogenated hydrocarbon e.g. dichloromethane or an alcohol e.g. tert-butanol
25 at a temperature from the ambient temperature to the reflux temperature.

Intermediate pyridines of formula (6) in Scheme 1 may be obtained by standard methods such as for example by the Sandmeyer reaction. Thus for example a bromide of formula (6) may be prepared by treatment of an aryl
30 amine of formula (7) with an alkyl nitrite, for example t-butyl nitrite and a copper salt, for example copper (II) bromide in the presence of a solvent, for

example a nitrile such as acetonitrile at a temperature from about 0° to around 65°C.

5 Amines of formula (7) may be formed from 2-halopyridine-2-carbonitriles of formula (8) by reaction with a reagent of formula $\text{HXCH}_2\text{CO}_2\text{Et}$ [where Et is an ethyl group and X is a -O- or -S- atom or -NH- group]. The reaction may be performed in the presence of a solvent such as a substituted amide for example dimethylformamide or an ether e.g. a cyclic ether such as tetrahydrofuran or alcohol such as ethanol in the presence of a base, for
10 example an inorganic base such as sodium carbonate or a hydride e.g. sodium hydride or an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene or a trialkylamine such as triethylamine at a temperature between about 0°C and 100°C. The carbonitrile starting materials are readily available or may be obtained from known compounds using standard procedures.

15

The intermediate pyridones of formula (4) are useful for obtaining other compounds of the invention using standard coupling or displacement reactions.

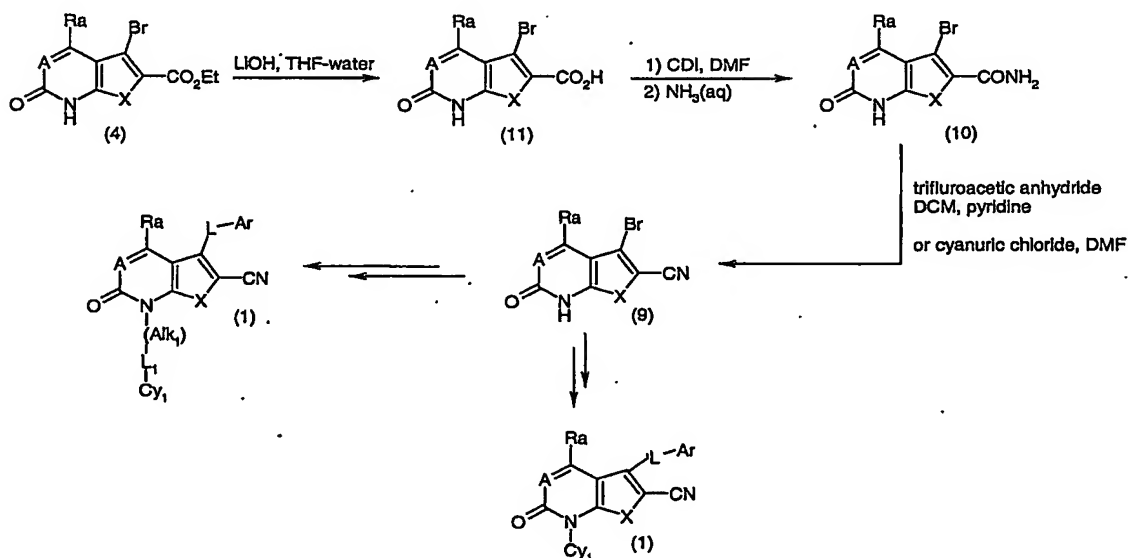
20 Thus for example palladium catalysed coupling such as described for the amination above additionally may be generally employed with a pyridone of formula (4) and any other amine, amide, urea and other appropriate starting materials $\text{Ar}(\text{CH}_2)_q\text{HetH}$ to obtain a compound of the invention.

25 In another example, compounds of formula (1) in which the ArL- group is linked to the remainder of the compound through a carbon atom may be obtained by palladium coupling using a reagent such as tetrakis(triphenylphosphine)palladium(0), an intermediate of formula (4), a halide $\text{Ar}(\text{CH}_2)_q\text{HetCH}_2\text{Hal}$ (where Hal is a halogen atom such as a bromine
30 atom) or $\text{Ar}(\text{CH}_2)_q\text{CR}^{3a}\text{R}^{3b}\text{Hal}$ and activated zinc in a solvent such as tetrahydrofuran at an elevated temperature.

In a further example, compounds of formula (1) in which L is a $-S(CH_2)_q-$ atom or chain may be obtained by displacement of the bromine atom in a pyridone of formula (4) using a thiol $Ar(CH_2)_qSH$ and a base such as potassium carbonate in a solvent such as dimethylformamide at an elevated temperature. Similarly, the bromine atom in a pyridone of formula (4) may be displaced using a compound $Ar(CH_2)_qOH$ in the presence of $Cu(II)O$, a base such as potassium carbonate and a solvent such as pyridine at an elevated temperature, to yield a compound of the invention in which L is a $-O(CH_2)_q-$ atom or chain.

In another process according to the invention, a compound of formula (1) in which A is a $-C(R^b)=$ group, X is a $-O-$ or $-S-$ atom or $-NH-$ group and Y is a $-C(CN)=$ group may be prepared using the reactions set out in Scheme 2 below:

Scheme 2



Thus in Scheme 2, a 2-cyano intermediate of formula (9) may be converted in a final step to a compound of the invention using the reactions and

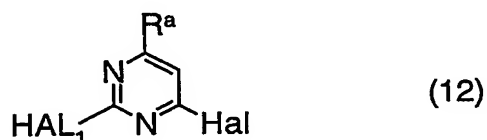
reagents described above in relation to the conversion of intermediates of formula (4) to compounds of the invention. Nitriles of formula (9) may be obtained by dehydration of the corresponding amide of formula (10) using a dehydrating agent such as trifluoroacetic anhydride in the presence of a base
5 such as pyridine in a solvent, for example a halogenated hydrocarbon such as dichloromethane at around ambient temperature. Alternatively, cyanuric

chloride may be used in a solvent such as dimethylformamide at a temperature from around 0°C to 110°C. Amides of formula (10) may be obtained from the corresponding acids of formula (11) using conventional
10 procedures, for example by reaction with 1,1'-carbonyldiimidazole and aqueous ammonia in a solvent such as dimethyl formamide at ambient temperature. The intermediate acids of formula (11) may be prepared by hydrolysis of esters of formula (4) using a base such as lithium hydroxide in water and a solvent such as tetrahydrofuran.

15

Compounds of formula (1) in which A is a -N= atom may be obtained using the synthetic routes in Schemes (1) and (2) with a pyrimidine starting material of formula (12):

20



wherein Hal₁ and Hal which may be the same or different is each a halogen atom such as a chlorine atom.

25 In this instance the final step in the synthesis of a compound of the invention may be hydrolysis of the Hal₁ atom using a base such as sodium or potassium hydroxide in a solvent such as an alcohol, e.g. methanol or

ethanol at an elevated temperature, e.g. the reflux temperature. Alternatively, the Hal atom may first be converted to an ether by reaction with an alkoxide such as sodium methoxide or sodium benzyloxide in a solvent, e.g. an alcohol such as methanol or ethanol at a temperature between 0°C and the
5 reflux, and the ether then cleaved using standard procedures such as by reduction with hydrogen gas in the presence of a catalyst such as a palladium catalyst, e.g. palladium on charcoal, or where the ether is an alkyl ether, by reaction with a trialkylsilyl halide such as trimethylsilyl chloride, optionally in the presence of an inorganic halide such as sodium iodide in a
10 solvent such as a halogenated hydrocarbon, e.g. dichloromethane or in a nitrile e.g. acetonitrile.

Compounds of the invention and intermediates thereto where A represents a $-N(R^b)-$ or $-C(R^b)(R^c)-$ group may be generated from corresponding
15 compounds of the invention or intermediates thereto where A represents a $-N=$ or $-C(R^b)=$ group by reduction, for instance by catalytic hydrogenation using a metal catalyst such as palladium on charcoal in the presence of hydrogen gas at an elevated pressure in a solvent such as an alcohol, e.g. ethanol optionally at an elevated temperature e.g. between 40°C and 60°C.

20 Where in the general processes described above intermediates such as alkylating agents of formula $Cy^1L^1(Alk^1)_nZ$, reagents of formula $HXCH_2CO_2Et$ and any other intermediates required in the synthesis of compounds of the invention are not available commercially or known in the literature, they may
25 be readily obtained from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be
30 appreciated that these methods may also be used to obtain or modify other

intermediates and in particular compounds of formula (1) where appropriate functional groups exist in these compounds.

Thus for example aromatic halogen substituents in the compounds may be
5 subjected to halogen-metal exchange with a base, for example a lithium base
such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around

-78°C, in a solvent such as tetrahydrofuran and then quenched with an
electrophile to introduce a desired substituent. Thus, for example, a formyl
group may be introduced by using dimethylformamide as the electrophile, a
10 thiomethyl group may be introduced by using dimethyldisulphide as the
electrophile, an alcohol group may be introduced by using an aldehyde as
electrophile and an acid may be introduced by using carbon dioxide as
electrophile. Aromatic acids of formula ArCO_2H may also be generated by
quenching Grignard reagents of formula ArMgHal with carbon dioxide.

15

Aromatic acids of formula ArCO_2H generated by this method and acid
containing compounds in general may be converted to activated derivatives,
e.g. acid halides by reaction with a halogenating agent such as a thionyl
halide e.g. thionyl chloride, a phosphorous trihalide such as phosphorous
20 trichloride or a phosphorous pentahalide such as phosphorous pentachloride
optionally in an inert solvent such as an aromatic hydrocarbon e.g. toluene or
a chlorinated hydrocarbon e.g. dichloromethane at a temperature from about
0°C to the reflux temperature, or may be converted into Weinreb amides of
formula $\text{ArC}(\text{O})\text{N}(\text{OMe})\text{Me}$ by conversion to the acid halide as just described
25 and subsequent reaction with an amine of formula $\text{HN}(\text{OMe})\text{Me}$ or a salt
thereof, optionally in the presence of a base such as an organic amine, e.g.
triethylamine in an inert solvent such as an aromatic hydrocarbon e.g.
toluene or a chlorinated hydrocarbon e.g. dichloromethane at a temperature
from about 0°C to ambient temperature.

30

Compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ group (where L^1 is a linker atom or group) may be treated with an alkylating agent Cy^1Z^2 in which Z^2 is a leaving atom or group such as a
5 halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

- 10 The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

15

In another example, compounds containing a $-L^2H$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with the alkylating agents just described but in which Z^2 is replaced by a $-C(O)Z^3$, $C(S)Z^3$, $-N(R^2)COZ^3$ or $-N(R^2)C(S)Z^3$ group in which Z^3 is a leaving
20 atom or group as described for Z^2 . The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the
25 acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in which Z^2 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [O-(7-azabenzotriazol-
30 1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-

hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

- 5 In a further example compounds may be obtained by sulphonylation of a
----- compound containing an -OH group by reaction with one of the above
alkylating agents but in which Z^2 is replaced by a $-S(O)Hal$ or $-SO_2Hal$ group
[in which Hal is a halogen atom such as chlorine atom] in the presence of a
base, for example an inorganic base such as sodium hydride in a solvent
10 such as an amide, e.g. a substituted amide such as dimethylformamide at for
example ambient temperature.

- In another example, compounds containing a $-L^2H$ group as defined above
may be coupled with one of the alkylation agents just described but in which
15 Z^2 is replaced by an -OH group in a solvent such as tetrahydrofuran in the
presence of a phosphine, e.g. triphenylphosphine and an activator such as
diethyl, diisopropyl- or dimethylazodicarboxylate.

- Ester groups such as $-CO_2Alk^6$ and $-CO_2R^4$ in the compound of formula (1)
20 and intermediates thereto may be converted to the corresponding acid [$-CO_2H$]
by acid- or base-catalysed hydrolysis depending on the nature of the
group Alk^6 or R^4 . Acid- or base-catalysed hydrolysis may be achieved for
example by treatment with an organic or inorganic acid, e.g. trifluoroacetic
acid in an organic solvent e.g. dichloromethane or a mineral acid such as
25 hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide,
e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

- In a further example, $-OR^6$ [where R^6 represents an alkyl group such as
methyl group] in compounds of formula (1) and intermediates thereto may be
30 cleaved to the corresponding alcohol -OH by reaction with boron tribromide in

a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C .

- 5 Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-\text{OCH}_2\text{R}^{31}$ group (where R^{31} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [e.g. -
- 10 CO_2Alk^6] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

- 15 In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-\text{OR}^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

- 20 Aminosulphonylamino [-NHSO₂NH₂] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

- 25 In another example compounds containing a $-\text{NHCSR}^7$ or $-\text{CSNHR}^7$ group may be prepared by treating a corresponding compound containing a $-\text{NHCOR}^7$ or $-\text{CONHR}^7$ group with a thiation reagent, such as Lawesson's Reagent or P_2S_5 , in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

30

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides for example sodium triacetoxyborohydride or sodium cyanoborohydride. The reduction may be
5 carried out in a solvent such as a halogenated hydrocarbon, e.g. ~~dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol,~~
where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon e.g. toluene and then
10 subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) and
15 intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$],
20 for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

25

In a further example amine ($-CH_2NH_2$) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles ($-CN$), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as
30 carbon, or Raney[®] nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran or an alcohol e.g. methanol or ethanol, optionally in

the presence of ammonia solution at a temperature from ambient to the reflux temperature, or by chemical reduction using for example a metal hydride e.g. lithium aluminium hydride, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

5

In another example, sulphur atoms in the compounds, for example when present in a group L, L¹ or L² may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

10

In a further example N-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base as described above in relation to the preparation of intermediates of formula (5).

15

Salts of compounds of formula (1) may be prepared by reaction of compounds of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

20

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

25

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and

30

the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

5 In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired, a particular enantiomer may be obtained by using an appropriate

chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer specific enzymatic biotransformation e.g. an ester hydrolysis using an esterase and
10 then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is
15 desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
20 MeOH - methanol;	BOC - butoxycarbonyl;
DCM - dichloromethane;	AcOH - acetic acid;
DIPEA - diisopropylethylamine;	EtOH - ethanol;
Pyr - pyridine;	Ar - aryl;
DMSO - dimethylsulphoxide;	iPr - isopropyl;
25 Et ₂ O - diethylether;	Me - methyl;
THF - tetrahydrofuran;	h - hour;
MCPBA - 3-chloroperoxybenzoic acid;	NBS - N-bromosuccinimide;
FMOC - 9-fluorenylmethoxycarbonyl;	r.t. - room temperature;
DBU - 1,8-Diazabicyclo[5,4-0]undec-7-ene;	
30 EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride;	
HOBT - 1-hydroxybenzotriazole hydrate;	

BINAP - 2,2'-bis(diphenylphosphino)-1-1'-binaphthyl;

DMF - N,N-dimethylformamide;

All NMRs were obtained either at 300MHz or 400MHz.

5

Compounds were named with the aid of either Beilstein Autonom supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany or ACD Labs Name (v.5.0) supplied by Avanced Chemical Development, Toronto, Canada.

10

LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following following method: Phenomenex Luna 3 μ C₁₈(2) 50x4.6mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of 0.9mLmin⁻¹, column temperature 40°C.

15

Gradient:-	Time	%B
	Initial	5
	2.00	95
	3.00	95
	5.0	5
	5.5	end

20

Intermediate 1

25 Ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of 2-chloro-3-cyanopyridine (330g), ethyl 2-mercaptoacetate (361.2g), sodium carbonate (265g) and EtOH (1.2L) was heated to reflux for 4.5 hours. It was then cooled to ambient temperature, added to water (10L) and the addition was washed in with water (5L). The resulting slurry was stirred for 30 minutes and then it was filtered. The filter cake was washed with two portions of water (2 x 2.5L) and dried at the pump. The solids were

30

then dried to constant weight under vacuum at 45°C to yield the title compound as a brown solid (493.1g, 93.2%). δ H (CDCl₃) 8.68 (1H, dd, \underline{J} 4.7, 1.2Hz), 7.93 (1H, dd, \underline{J} 8.5, 1.2Hz), 7.29 (1H, dd, \underline{J} 8.5, 4.7Hz), 5.90 (2H, b), 4.38 (2H, q, \underline{J} 7.0Hz), 1.40 (3H, t, \underline{J} 7.0Hz). LCMS RT 2.9 minutes, 223
5 (M+H)⁺

Intermediate 2

Ethyl 3-bromothieno[2,3-*b*]pyridine-2-carboxylate

Intermediate 1 (363.6g) was added in portions over two hours to a mixture of
10 copper(II) bromide (403.3g), t-butyl nitrite (220.6g) and acetonitrile (3.6L)
stirred at a temperature of 20 to 25°C. The mixture was stirred at 20°C for 2
hours before it was slowly added to 2M HCl(aq) (4.2L). The reaction mixture
slurry was filtered and the solids were washed with water (500mL). The
combined filtrate was extracted with ethyl acetate (8L), this ethyl acetate
15 solution was washed with 2M HCl(aq) (2.2L). The solids were dissolved in
ethyl acetate (6L), this solution was washed twice with 2M HCl(aq) (4.4L and
2.2L). The two ethyl acetate solutions were then combined and washed with
2M HCl(aq) (2.2L) and twice with water (2 x 2L). The ethyl acetate solution
was the dried (MgSO₄), filtered and concentrated *in vacuo* at 40 mbar and
20 60°C to give a solid residue. This was broken up and dried to constant
weight under vacuum at 45°C to yield the title compound as a brown solid
(458.5g, 97.9%). δ H (DMSO-d₆) 8.89 (1H, d, \underline{J} 4.7Hz), 8.47 (1H, d, \underline{J} 8.6Hz),
7.71 (1H, dd, \underline{J} 8.6, 4.7Hz), 4.46 (2H, q, \underline{J} 7.2Hz), 1.40 (3H, t, \underline{J} 7.2Hz).
LCMS RT 3.8 minutes, 288 (M+H)⁺

25

Intermediate 3

Ethyl 3-Bromothieno[2,3-*b*]pyridine-2-carboxylate N-oxide

To a slurry of Intermediate 2 (214g, 0.747Mol) in DCM (2140mL) under
nitrogen was added MCPBA (240g @ 70% = 168g, 0.97Mol) portion wise
30 over 0.5h. The reaction was then stirred at room temperature for 18h. The
reaction mixture was quenched with water (800mL) and pH adjusted to 8.5

with 10%w/v sodium carbonate solution (1250mL). The basic aqueous layer was removed and the organic layer washed with water until pH 7. The organic layer was concentrated *in vacuo* and the crude title product was recovered as a tan solid. The crude product was purified by slurrying in
5 MTBE (600mL) for 1h at 0-5°C to give the title compound (174g, 77%). δ H (CDCl₃) 8.44 (1H, dd, \underline{J} 6.2, 0.8Hz), 7.87 (1H, dd, \underline{J} 8.3, 0.8Hz), 7.48 (1H, dd, \underline{J} 8.3, 6.2Hz), 4.49 (2H, q, \underline{J} 7.1Hz), 1.48 (3H, t, \underline{J} 7.1Hz). LCMS (ES⁺) RT 2.61 minutes, 302(M+H)⁺

10 Intermediate 4

Ethyl 3-bromo-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

A mixture of Intermediate 3 (500mg, 1.66mmol) and DMF (10mL) was set to stir at 0°C under nitrogen. To this reaction mixture was added trifluoroacetic anhydride (3.49g, 2.36mL, 16.6mmol) in one portion via syringe. After stirring
15 for 16 hours the volatiles were removed *in vacuo* and the residue co-evaporated with toluene (2x20mL). The crude material was then extracted with EtOAc (2x100mL). The EtOAc extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by a re-slurry in toluene (10mL) to give the title compound as a beige solid (260mg, 52%). δ H
20 (DMSO-d₆) 12.20 (1H, brs), 7.75 (1H, d, \underline{J} 9.0Hz), 6.50 (1H, d, \underline{J} 9.0Hz), 4.15 (2H, q, \underline{J} 7.1Hz), 1.12 (3H, t, \underline{J} 7.1Hz). LCMS (ES⁺) RT 2.86 minutes, 302 ((M+H)⁺, 100%). MP = 261.7-268.1°C.

Intermediate 5

25 Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

To a 2 necked round bottomed flask was added in sequence Intermediate 4 (302mg, 1.00mmol), copper(II) acetate (278mg, 1.50mmol), phenylboronic acid (488mg, 4.00mmol), DCM (5mL) and pyridine (158mg, 2.00mmol). The
30 reaction was stirred at room temperature for 18h with the exclusion of moisture. The reaction was then diluted with DCM (50mL), washed with 2M

HCl(aq) (50mL), the aqueous was re-extracted with DCM (50mL). The combined organics were then washed with water (50mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by a slurry in methanol (12mL), to give the title compound as a beige solid (270mg, 72%).

5 δ H (CDCl₃) 7.82 (1H, d, \downarrow 8.5Hz), 7.70-7.62 (3H, m), 7.54-7.42 (2H, m), 6.70
----- (1H, d, \downarrow 8.5Hz), 4.15 (2H, q, \downarrow 7.1Hz), 1.14 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT
3.75 minutes, 378 (M+H)⁺. MP = 201.6-206.0°C.

10 Example 1

Ethyl 3-(benzylamino)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

Tris(dibenzylideneacetone)dipalladium(0) (12mg, 0.0133mmol, 5mol%) was added to a mixture of Intermediate 5 (100mg, 0.265mmol), caesium carbonate (120mg, 0.37mmol), benzylamine (0.035mL, 0.32mmol) and
15 BINAP (17mg, 0.027, 10mol%) in anhydrous toluene (2mL) and the reaction heated to reflux under nitrogen for 18h. Solvent was removed *in vacuo* and the crude residue purified by chromatography on silica (0-20% EtOAc in DCM) to give the title compound as a white solid (52mg). δ H (CDCl₃) 7.80
20 (1H, bs), 7.72 (1H, d, \downarrow 9.9Hz), 7.60-7.48 (3H, m), 7.28-7.10 (7H, m), 6.37 (1H, d, \downarrow 9.9Hz), 4.73 (2H, bd, \downarrow 4.5Hz), 4.14 (2H, q, \downarrow 7.1Hz), 1.18 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 4.03 minutes, 405 (M+H)⁺.

General procedure for the preparation of Ethyl 3-benzylamino-6-oxo-7-phenyl-6,7-tetrahydrothieno[2,3-b]pyridine-2-carboxylates

25 The compounds of Examples 2-4 were prepared by parallel synthesis using a Radleys Carousel reaction station (Radleys Ltd., Saffron Walden, U.K.) following a procedure similar to that described for Example 1. Therefore to each oven dried reaction tube in the Carousel was added a magnetic stirrer,
30 the appropriate substituted aniline or benzylamine (0.64mmol), anhydrous toluene (3mL), Intermediate 5 (200mg, 0.53mmol), caesium carbonate

(
(240mg, 0.74mmol) and tris(dibenzylideneacetone)dipalladium(0) (48mg, 0.053mmol, 10mol%). The reactions were heated to reflux under nitrogen and with magnetic stirring for 48h. Each reaction was then diluted with DCM (10mL), washed with water (10mL), dried (MgSO₄) and concentrated *in vacuo*. The crude products were purified on silica eluting with 0-20% EtOAc in DCM to give the title compounds as solids.

Example 2

Ethyl 3-[benzyl(methyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

From N-methylbenzylamine to give the title compound (95mg). δ H (CDCl₃) 7.73 (1H, d, \downarrow 9.6Hz), 7.58-7.41 (3H, m), 7.36-7.14 (7H, m), 6.52 (1H, d, \downarrow 9.6Hz), 4.43 (2H, s), 4.17 (2H, q, \downarrow 7.1Hz), 2.89 (3H, s), 1.21 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 4.19 minutes, 419 (M+H)⁺.

Example 3

Ethyl 6-oxo-3-[(1-phenylethyl)amino]-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

From alpha-methylbenzylamine to give the title compound (149mg). δ H (CDCl₃) 7.83 (1H, bd, \downarrow 7.6Hz), 7.58 (1H, d, \downarrow 9.9Hz), 7.54-7.36 (3H, m), 7.32-7.14 (7H, m), 6.27 (1H, d, \downarrow 9.9Hz), 4.98 (1H, quintet, \downarrow 6.8Hz), 4.18 (2H, q, \downarrow 7.1Hz), 1.58 (3H, d, \downarrow 6.8Hz), 1.21 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 4.19 minutes, 419 (M+H)⁺.

Example 4

Ethyl 3-[(2,6-difluorobenzyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

From 2,6-difluorobenzylamine to give the title compound (130mg). δ H (CDCl₃) 8.04 (1H, d, \downarrow 9.9Hz), 7.61-7.40 (3H, m), 7.39-7.25 (3H, m), 7.38-7.14 (1H, m), 6.93-6.78 (2H, m), 6.54 (1H, d, \downarrow 9.9Hz), 4.73 (2H, d, \downarrow 6.0Hz), 4.10 (2H, q, \downarrow 7.1Hz), 1.15 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 3.98 minutes, 441 (M+H)⁺.

Example 5

Ethyl 3-benzyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

Benzyl bromide (0.040mL, 0.317mmol) was added to activated zinc powder
5 (26mg, 0.397mmol) in anhydrous THF (2mL) under nitrogen and the mixture
heated-to-reflux-for-2h. The reaction was cooled to r.t. and Intermediate 5
(100mg, 0.265mmol) and tetrakis(triphenylphosphine)palladium(0) (30mg,
0.026mmol, 10mol%) added to the reaction mixture. The reaction was then
heated to reflux for 18h with two further portions of Pd(PPh₃)₄ (30mg) added
10 at intervals during the reaction. The reaction was partitioned between EtOAc
and water and the EtOAc extracts dried (MgSO₄) and concentrated *in vacuo*.
The crude product was purified by chromatography on silica (0-20%EtOAc in
DCM) to give the title compound as a white solid (87mg). δ H (CDCl₃) 7.69
(1H, d, \downarrow 9.6Hz), 7.67-7.30 (3H, m), 7.25-7.18 (2H, m), 7.20-7.00 (5H, m),
15 6.51 (1H, d, \downarrow 9.6Hz), 4.51 (2H, s), 4.21 (2H, q, \downarrow 7.2Hz), 1.22 (3H, t, \downarrow
7.2Hz). LCMS (ES⁺) RT 3.92 minutes, 390 (M+H)⁺.

Example 6

Ethyl 6-oxo-3-phenoxy-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-

carboxylate

A mixture of Intermediate 5 (500mg, 1.32mmol), phenol (137mg, 1.46mmol),
Cu(II)O (209mg, 1.46mmol) and K₂CO₃ (221mg, 1.60mmol) in pyridine
(10mL) was heated at 115°C for 18h. The reaction was cooled to r.t., 2M
HCl(aq) (30mL) added and the aqueous extracted with EtOAc (3x20mL). The
25 combined EtOAc extracts were washed with 2M HCl(aq), brine, dried
(MgSO₄) and concentrated *in vacuo*. The crude product was purified by
chromatography on silica (0-10% EtOAc in DCM) to give the title compound
as a solid (110mg). δ H (CDCl₃) 7.61-7.43 (3H, m), 7.42-7.29 (3H, m), 7.28-
7.18 (2H, m), 7.00 (1H, t, \downarrow 7.4Hz), 6.92 (2H, d, \downarrow 7.8Hz), 6.49 (1H, d, \downarrow
30 9.6Hz), 4.08 (2H, q, \downarrow 7.1Hz), 1.04 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 3.81
minutes, 392 (M+H)⁺

Example 7

Ethyl 6-oxo-7-phenyl-3-phenylsulfanyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate

- 5 A mixture of Intermediate 5 (500mg, 1.32mmol), thiophenol (0.15mL, 1.46mmol) and K₂CO₃ (221mg, 1.60mmol) in DMF (10mL) was heated at 80°C under nitrogen for 18h. The reaction was cooled to r.t., diluted with water and the aqueous extracted with EtOAc (3x20mL). The combined EtOAc extracts were washed with water, brine, dried (MgSO₄) and
- 10 concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-5% EtOAc in DCM) to give the title compound as a solid (150mg). δ H (CDCl₃) 7.58-7.48 (3H, m), 7.46 (1H, d, \downarrow 9.7Hz), 7.36-7.29 (2H, m), 7.25-7.07 (5H, m), 6.44 (1H, d, \downarrow 9.7Hz), 4.21 (2H, q, \downarrow 7.1Hz), 1.20 (3H, t, \downarrow 7.1Hz). LCMS (ES⁺) RT 3.97 minutes, 408 (M+H)⁺

15

The following assays and animal models can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each assay an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition.

20

Preparation of activated human p38 α for inhibitor assays.

Purification of human p38 α

- Human p38 α , incorporating an N-terminal (His)₆ tag, was expressed in
- 25 baculovirus-infected High-Five™ cells (Invitrogen) according to the manufacturers instructions. The cells were harvested 72h post-infection and lysed in phosphate buffered saline (PBS) containing 1% (w/v) β -octylglucoside and Complete, EDTA-free™ protease inhibitors (Roche Molecular Biochemicals). The lysate was centrifuged at 35000xg for 30min at
- 30 4°C and the supernatant applied to a NiNTA™ column (Qiagen). Bound protein was eluted by 150mM imidazole in PBS (after a wash with 15mM

imidazole in PBS) and directly applied to a HiTrap Q™ column (AP Biotech). Bound protein was eluted using a 20 column volume, 0 to 1M NaCl gradient. Fractions containing (His)6-p38 were aliquotted and stored at -70° prior to their activation.

5

Preparation of GST-MKK6EE-containing lysates

E. coli (BL21 pLysS) expressing the constitutively activated form of human MKK6 fused with an N-terminal glutathione-S-transferase tag (GST-MKK6EE) were harvested by centrifugation and frozen at -70°. Cells were
10 lysed by resuspension in 1/10th the culture volume of PBS containing Complete, EDTA-free™ protease inhibitors followed by sonication on ice for 4x15 sec. Cell debris was removed by centrifugation at 35,000xg and the resultant supernatant stored in aliquots at -70°.

15 Activation of (His)6-p38

0.45mL of purified (His)6-p38 was incubated with 50µL of the GST-MKK6EE-containing lysate for 30min at 23° in the presence of 1mM β-glycerophosphate, 10mM MgCl₂ and 9mM ATP. The extent of activation was monitored by mass spectrometric detection of the doubly-phosphorylated
20 form of (His)6-p38, which routinely comprised greater than 90% of the final (His)6-p38 preparation. The activated (His)6-p38 was then diluted x10 in PBS and repurified using the method described above. The concentration of purified, activated (His)6-p38 was measured by UV absorbance at 280nm using $A_{280} \cdot 0.1\% = 1.2$ and the preparation stored in aliquots at -70° prior to
25 its use in inhibitor assays.

p38 Inhibition Assays

Inhibition of phosphorylation of biotinylated myelin basic protein (MBP)

The inhibition of p38 catalysed phosphorylation of biotinylated MBP is
30 measured using a DELFIA based format. The assay was performed in a buffer comprising, 20mM HEPES (pH 7.4), 5mM MgCl₂ and 3mM DTT. For a

typical IC₅₀ determination, biotinylated MBP (2.5µM) was incubated at room temperature in a streptavidin-coated microtitre plate together with activated gst-p38 (10nM) and ATP (1µM) in the presence of a range of inhibitor concentrations (final concentration of DMSO is 2 percent). After fifteen minutes the reaction was terminated by the addition of EDTA (75mM). The microtitre plate was then washed with Tris buffered saline (TBS), prior to the addition of 100µl of anti-phospho MBP antibody (mouse) together with europium-labeled anti-mouse IgG antibody. After one hour at room temperature the plate was again washed in TBS followed by the addition of Enhancement solution (PerkinElmer Wallac). Fluorescence measurements were performed after a further fifteen minutes at room temperature.

IC₅₀ values are determined from the plot of Log₁₀ inhibitor concentration (x-axis) versus percentage inhibition of the fluorescence generated by a control sample in the absence of inhibitor (y-axis).

Purification of human Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMC) were isolated from normal healthy volunteers. Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), diluted 1 in 4 in RPMI 1640 (Gibco, UK) and centrifuged at 400g for 35 min over a Ficoll-paque gradient (Amersham-Pharmacia Biotech, UK). Cells at the interface were removed and washed once followed by a low speed spin (250g) to remove platelets. Cells were then resuspended in DMEM containing 10% FCS, penicillin 100 units ml⁻¹, streptomycin 50µg ml⁻¹ and glutamine 2mM (Gibco, UK).

Inhibitor dilutions

Inhibitor stocks (20mM) were kept as a frozen solution (-20°C) in DMSO. Serial dilutions of inhibitors were performed in DMSO as 250-times concentrated stocks. Inhibitors were diluted 1 in 250 into tissue culture media, prewarmed to 37°C and transferred to plates containing PBMC.

PBMC and inhibitors were incubated together for 30 mins prior to addition of LPS. Inhibitors used in whole blood assays were prepared according to a different regime. Using the same stock solution serial dilutions of inhibitors were performed in DMSO. Inhibitors were then diluted 1 in 500 straight into whole blood in a volume of 1µL. Inhibitor was incubated with whole blood for 30 mins prior to the addition of LPS.

LPS stimulation of PBMC

PBMC were resuspended at a density of 2×10^5 cells/well in flat bottomed 96 well tissue culture treated plates. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final concentration of $1 \mu\text{g ml}^{-1}$) and incubated at 37°C in 5%CO₂/95% air for 18 hours. TNF-α levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

15

LPS stimulation of whole blood

Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), and 500µl of blood aliquoted into each well of a 24 well tissue culture treated plate. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E coli* strain B5:055, Sigma, at a final concentration of $1 \mu\text{g ml}^{-1}$) and incubated at 37°C without CO₂ for 18 hours. TNF-α levels were measured from cell free supernatants by sandwich ELISA (BioSource #CHC1751).

20

Rat LPS induced TNF release

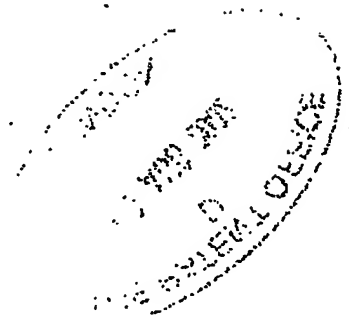
Male Lewis rats (180-200g) are anaesthetised with Isofluror and injected i.v. with LPS* in a volume of 0.5ml sterile saline. After 90minutes blood is collected into EDTA tubes for preparation of plasma samples. Plasma is stored at -70°C prior to assay for TNFα by commercial ELISA.

30

Rat CIA

Female Lewis rats (180-200g) are anaesthetised with Isofluror and immunised i.d. at the base of the tail with 2x100 μ l of emulsion containing 4mg/ml bovine collagen II in 0.01M acetic acid and Freund's Incomplete Adjuvant at a ratio of 1:1. A polyarthritis develops with onset from about 13 days post sensitisation. The disease is mainly confined to the ankles and is quantified by plethysmometry. Results are expressed as change in paw volume over time.

- 10 In the p38 inhibitor assays described above compounds of the invention have IC_{50} values of around 1 μ M and below. The compounds of the invention are clearly potent inhibitors of p38 kinase, especially p38 α kinase.



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